We Claim:

1. A method for identifying modified amino acids within a protein, comprising:

   (i) providing one or more samples and an affinity capture reagent for isolating, from said samples, those proteins post-translationally modified by a moiety of interest;

   (ii) processing said samples to chemically modify at least one of the C-terminal carboxyl, the N-terminal amine and amino acid side chains of polypeptides in said samples so as to increase the specificity of said affinity capture reagent for those proteins post-translationally modified by said moiety of interest;

   (iii) isolating said proteins post-translationally modified by said moiety of interest from said samples using said affinity capture reagent;

   (iv) eluting said proteins bound to said affinity capture reagent by manipulating the oxidation state of said affinity capture reagent; and,

   (v) determining the identity of said proteins eluted in (iv) by mass spectroscopy.

2. The method of claim 1, wherein said polypeptides in said samples are further cleaved into smaller peptide fragments before, after or during the step of processing said samples.

3. The method of claim 2, wherein said polypeptides are fragmented by enzymatic hydrolysis to produce peptide fragments having carboxy-terminal lysine or arginine residues.

4. The method of claim 3, wherein said polypeptides are fragmented by treatment with trypsin.

5. The method of claim 1, wherein said polypeptides are mass-modified with isotopic labels before, after or during the step of processing said samples.

6. The method of claim 1, wherein said proteins isolated in steps (iii) / (iv) are further separated by reverse phase chromatography before analysis by mass spectroscopy.

7. The method of claim 1, wherein said proteins isolated in steps (iii) and (iv) are identified from analysis using tandem mass spectroscopy techniques.

8. The method of claim 1, wherein step (v) is effectuated by searching molecular weight databases for the molecular weight observed by mass spectroscopy for an isolated protein or peptide fragment thereof.

9. The method of claim 1 or 7, further comprising obtaining amino acid sequence mass spectra for said proteins or peptide fragments thereof, and searching one or more sequence databases for the sequence(s) observed for said protein or peptide fragments thereof.

10. The method of claim 1, wherein said moiety of interest is a phosphate group.

11. The method of claim 10, wherein said affinity capture reagent is an immobilized metal affinity chromatography medium, and step (ii) includes chemically modifying the side chains of glutamic acid and aspartic acid residues to neutral derivatives.

12. The method of claim 11, wherein the side chains of glutamic acid and aspartic acid residues are modified by alkyl-esterification.

13. The method of claim 1, wherein said sample comprises a mixture of different proteins.

14. The method of claim 13, wherein said sample is derived from a biological fluid, or a cell or tissue lysate.

15. The method of claim 1, wherein said one or more samples comprise two or more different samples, and wherein the polypeptides or fragments thereof of each sample are isotopically labeled in a manner which permits discrimination of mass spectroscopy data between different samples.

16. A method for analyzing a phosphoproteome, comprising:

(i) providing one or more protein sample(s);

(ii) chemically modifying the side chains of glutamic acid and aspartic acid residues of polypeptides in said protein sample(s) to neutral derivatives;

(ii) isolating phosphorylated proteins from said protein sample(s) by using immobilized metal affinity chromatography;

(iii) eluting said phosphorylated proteins from said affinity capture reagent by manipulating the oxidation state of said reagent; and,

(iv) determining the identity of said phosphorylated proteins eluted in (iii) by mass spectroscopy.

17. The method of claim 16, further comprising cleaving said polypeptides into smaller peptide fragments, before, after or during the step of chemically modifying the glutamic acid and aspartic acid residues.

18. The method of claim 17, wherein said polypeptides are fragmented by enzymatic hydrolysis to produce peptide fragments having carboxy-terminal lysine or arginine residues.

19. The method of claim 18, wherein said polypeptides are fragmented by treatment with trypsin.

20. The method of claim 16, wherein the glutamic acid and aspartic acid residues are modified by alkyl-esterification.

21. The method of claim 16, wherein said one or more sample(s) comprise two or more different samples, the method further comprises identifying proteins which are differentially phosphorylated between said two or more different samples.

22. The method of claim 16 or 21, further comprising generating or adding to a database the identity of proteins which are determined to be phosphorylated.

23. A method for identifying a treatment that modulates a modification of amino acid in a target polypeptide, comprising:

(i) providing a sample which has been subjected to a treatment of interest;

(ii) determining, using the method of claim 1, the identity of proteins which are differentially modified in said treated sample relative to an untreated sample or control sample;

(iii) determining, whether said treatment results in a pattern of changes in protein modification which meets a preselected criterion, in said treated sample relative to said untreated sample or control sample.

24. The method of claim 23, wherein said treatment is effected by a compound.

25. The method of claim 24, wherein said compound is a growth factor, a cytokine, a hormone, or a small chemical molecule.

26. The method of claim 24, wherein said compound is from a chemical library.

27. The method of claim 23, wherein said sample is derived from a cell or tissue subjected to said treatment of interest.

28. A method of conducting a drug discovery business, comprising:

(i) determining, by the method of claim 24, the identity of a compound that produces a pattern of changes in protein modification which meet a preselected criterion, in said treated sample relative to said untreated sample or control sample;

(ii) conducting therapeutic profiling of said compound identified in step (i), or further analogs thereof, for efficacy and toxicity in animals; and,

(iii) formulating a pharmaceutical preparation including one or more compound(s) identified in step (ii) as having an acceptable therapeutic profile.

29. The method of claim 28, including an additional step of establishing a distribution system for distributing the pharmaceutical preparation for sale, and may optionally include establishing a sales group for marketing the pharmaceutical preparation.

30. A method of conducting a drug discovery business, comprising:

(i) determining, by the method of claim 24, the identity of a compound that produces a pattern of changes in protein modification which meet a preselected criterion, in said treated sample relative to said untreated sample or control sample;

(ii) licensing, to a third party, the rights for further drug development of compounds that alter the level of modification of the target polypeptide.

31. A method of conducting a drug discovery business, comprising:

(i) by the method of claim 1, determining the identity of a protein that is post-translationally modified under conditions of interest;

(ii) identify one or more enzymes which catalyze the post-translational modification of the identified protein under the conditions of interest;

(iii) conduct drug screening assays to identify compounds which inhibit or potentiate the enzymes identified in step (ii) and which modulate the post-translational modification of the identified protein under the conditions of interest.